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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/713,546
Filing Date: November 14, 2003
Appellant(s): HOFLAND, HANS E. J.

Joseph R. Snyder
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4-14-08 appealing from the Office action mailed 8-16-07.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,747,536	CAVAZZA	5-1998
6,726,924	KELLER	4-2002

5,993,851	FOLDVARI	11-1999
4,968,719	BREVETTI	11-1990

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cavazza (5,747,536) in view of Keller (6,726,924) or Foldvari (5,993,851) individually or in combination.

Cavazza teaches the effectiveness of L-carnitine and its esters in the treatment of peripheral vascular diseases. The derivatives taught by Cavazza are acetyl L-carnitine and propionyl L-carnitine (abstract, columns 3-5 and claims).

What is lacking in Cavazza is the use of liposomes as the delivery vehicles for carnitines.

Keller discloses that liposomes are sustained release delivery vehicles for a variety of active agents including L-carnitine. According to Keller, liposomes increase the bioavailability of active agents when administered (col. 2, lines 13-65).

Foldvari while disclosing liposomal formulations containing various biologically active agents for topical delivery teaches that several studies showed that liposome encapsulation advantageously alters the pharmacokinetic fate of the drug after topical application (abstract, col. 1, lines 49-52) and that liposomes (containing active agent, PGE1) can be used to treat diseases including peripheral vascular disease (col. 27, lines 41-47).

The use of liposomes as the delivery vehicles for the compositions of Brevetti would have been obvious to one of ordinary skill in the art since Keller teaches that liposomes are sustained release delivery vehicles and increase the bioavailability of active agents and Foldvari teaches that the topical delivery of liposomes can be used to treat peripheral vascular diseases. Alternately to use liposomes for the encapsulation of L-carnitine or its esters for treatment of peripheral vascular diseases would have been obvious to one of ordinary skill in the art since L-carnitine and its esters are effective against this disease as taught by Brevetti. One of ordinary skill in the art would expect the advantages of liposomes in the delivery of L-carnitine.

2. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brevetti (4,968,719) in view of Keller (6,726,924) or Foldvari (5,993,851) individually or in combination, further in view of Cavazza cited above.

Brevetti teaches L-carnitine's effectiveness for the treatment of peripheral vascular diseases (abstract, Examples and claims).

What is lacking in Brevetti is the use of liposomes as the delivery vehicles for Carnitine and the use of claimed derivatives of carnitine.

Keller discloses that liposomes are sustained release delivery vehicles for a variety of active agents including L-carnitine. According to Keller, liposomes increase the bioavailability of active agents when administered (col. 2, lines 13-65).

Foldvari while disclosing liposomal formulations containing various biologically active agents for topical delivery teaches that several studies showed that liposome encapsulation advantageously alters the pharmacokinetic fate of the drug after topical

application (abstract, col. 1, lines 49-52) and that liposomes (containing active agent, PGE1) can be used to treat diseases including peripheral vascular disease (col. 27, lines 41-47).

Cavazza as pointed out above teaches the effectiveness of L-carnitine and its esters in the treatment of peripheral vascular diseases. The derivatives taught by Cavazza are acetyl L-carnitine and propionyl L-carnitine (abstract, columns 3-5 and claims).

The use of liposomes as the delivery vehicles for the compositions of Brevetti would have been obvious to one of ordinary skill in the art since Keller teaches that liposomes are sustained release delivery vehicles and increase the bioavailability of active agents and Foldvari teaches that the topical delivery of liposomes can be used to treat peripheral vascular diseases. The use of the claimed derivatives of carnitine would have been obvious to one of ordinary skill in the art since Cavazza teaches the use of these derivatives for the treatment of the same disease.

(10) Response to Argument

REJECTION 1:

Applicant's arguments have been fully considered, but are not persuasive. Applicant argues that Cavazza actually teaches away from the use of a pharmaceutical composition comprising alkyl-L-carnitine alone as the active agent for the treatment of peripheral arterial disease as presently claimed. Applicant further argues the following. "Cavazza describes that the pathological basis of cardiovascular diseases, peripheral vascular diseases and diabetic peripheral neuropathy is undesired platelet aggregation.

Cavazza performed *in vitro* platelet aggregation tests to quantify the inhibitory effects of, *inter alia,* L-carnitine alone, resveratrol alone (a trihydroxy-stilbene), and combination thereof on platelet aggregation and used these results to evaluate the potential effectiveness of these compounds for treating various disease, including cardiovascular diseases, peripheral vascular diseases, and diabetic peripheral neuropathy. In short, Cavazza discloses that L-carnitine, when used by itself, was *completely ineffective* at inhibiting platelet aggregation. The disclosure of Cavazza would clearly suggest to a skilled artisan that a composition comprising L-carnitine alone *is not* effective at treating the aforementioned diseases since Cavazza clearly teaches that L-carnitine (or derivatives thereof) alone does not inhibit platelet aggregation. Specifically, Cavazza teaches at column 4, lines 51- 62, [Platelet] [a]ggregation was measured in basal conditions and after 10 minutes of incubation with L-carnitine, resveratrol, grape extract, and combinations of these preparations. Inhibition of the platelet aggregation induced by collagen (2. 5 ng/ml) proved evident (ED50 3. 5 ng/ml) for resveratrol and for grape extract (EDso with a resveratrol concentration equal to Z 5 ng/l), whereas for carnitine or its derivatives there was no significant change. However, when using a combination of the carnitines plus resveratrol at the same doses, 100% inhibition of platelet aggregation was achieved, thus showing a marked synergism between L-carnitine and resveratrol or grape extract containing resveratrol. [Emphasis added.] As stated above, Cavazza clearly discloses that L-carnitine (or derivatives thereof) alone would not be effective in treating peripheral vascular diseases such as peripheral arterial disease as is presently claimed by Appellant, and actually teaches away from this use alone."

These arguments are not found to be persuasive. First of all, instant claim language does not exclude other components taught by Cavazza and Cavazza teaches 100 % inhibition of platelet aggregation of the carnitine esters and resveratrol (col. 5, line 1 et seq.). Secondly, Cavazza' teachings are not based on platelet aggregation alone. On col. 3, lines 50-56, Cavazza teaches that L-carnitine and particularly propionyl L-carnitine can act by varying the lipid substrate from which come, as a result of the action of cyclooxygenases and lipo-oxygenases, the various vasoconstricting and pro-aggregation factors, reducing their formation and facilitating the synthesis of anti-aggregating and vasodialatory factors. Synergism means that each component has some effect and when combined, the effect is more than additive. Instant application does not contain any data to show that claimed compounds have any effect on claimed disease condition. Applicant's arugments that Keller is directed to oral liposomal delivery system, but does not teach claimed alkyl-carnitine are not persuasive since instant claims do not recite the mode of administration and since Keller is combined to show that liposomes increase the bioavailability of the administered compounds which include carnitine and one would expect the increase in bioavailability of any compound including the derivatives of carnitine. One of ordinary skill in the art would be motivated to encapsulate instant compounds based on Foldvari, which teaches liposomal administration of active agents for the treatment of peripheral arterial diseases.

REJECTION 2:

Applicant's arguments have been fully considered, but are not persuasive. The examiner has already addressed applicant's arguments regarding Cavazza, Keller, and

Foldvari. Applicant's only argument is that Brevetti's reference does not supplement the deficiencies of the other cited references, namely the use of certain alkyl-L-carnitine derivatives as the active agent in treating peripheral arterial disease, much less a liposomal formulation of these alkyl--L-carnitine as is presently claimed by appellant. This argument is not persuasive since the effectiveness of carnitine and its esters in the treatment of peripheral arterial disease is clearly evident from Brevetti and Cavazza respectively.

(11) Related Proceeding(s) Appendix

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Gollamudi S Kishore, Ph.D/

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